Firstly, the Examiner has objected to claims 34-35, contending improper dependence according to previous amendments. Claims 34 and 35 are amended herein and shown to be so in the "marked up version of the claims", as requested by the Examiner. Claims 34 and 35 now depend from claim 31. Therefore the Examiner's objection to these claims should be withdrawn.

Secondly, claims 1, 4, 5, 10-13, 16-17, 19-20, 22-27, 29-32 and 38 are rejected as being unpatentable over McCasky '030 in view of McGall '501. These rejections are respectfully traversed.

In the present application, particular claims are drawn to a substrate having a surface area, the surface area comprising attached labeled probe molecules, said labeled probe molecules having therein incorporated nucleotide analogs that fluoresce and whose decrease in florescence, when substantially approaching zero, provide for the quantification of complementary molecules, hybridized to labeled probe molecules, by quenching a first florescence. Substrates that provide target/probe pair quantification are neither taught or suggested by McCasky '030, particularly a quenching of fluorescence substantially approaching zero/background levels being utilized to provide for resultant quantification. In addition to the lack of these teachings, Applicant's respectfully point out that the Examiner had also conceded that McCasky '030 ***does not teach*** nucleotide analogs or arrays divided into quadrants, or methods wherein the levels of label are expressed twice and compared or labeled probes achieved by non-amplification steps.

Such substrates and associated methods for quantification of target/complementary molecules are simply not contemplated by McCasky '030. Additionally, McGall '501 does not remedy the lack of these teachings. For example and referring to pending independent Claim 37, there is no teaching or suggestion in either McCasky '030 or McGall '501 of a method step of identifying probe and target hybridized molecules by repeating steps c-f (see Claim 37) until the amounts of label expression between the first and second levels of label approaches zero and/or about background levels.

As neither McCasky '030 nor McGall '501, alone or in combination, teach or suggest the invention as presently claimed, Applicant respectfully requests that Examiner withdraw all pending 35 U.S.C. 103 rejections.

The scope and content of the prior art cited against dependent claims 7, 14, 15 and 18, fails to remedy the lack of initial teachings of McCasky '030 and McGall '501 and as such rejections to these claims should also be withdrawn.

Applicant is also concurrently filing an Information Disclosure Statement, listing new references cited by the Examiner during said interview, with the submission of this Amendment.

In conclusion and in view of the above, it is submitted that this application is now in good order for allowance, and such early action is respectfully solicited. Should matters remain which the Examiner believes could be resolved in a telephone interview, the Examiner is requested to telephone the Applicant's undersigned agent.

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1561.

Respectfully submitted,

Date: January 8, 2003

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ADDENDUM PAGES

SET OF MARKED-UP CLAIMS WITH UNDERLINING AND BRACKETS

1. (Twice Amended) A substrate having a surface area, the surface area comprising attached labeled probe molecules, said labeled probe molecules having therein incorporated nucleotide analogs that fluoresce and whose decrease in florescence, when substantially approaching zero,[being for measuring or detecting] quantifies the presence or hybridization of complementary molecules to the labeled probe molecules by quenching a first florescence provided by the labeled probe molecules.

16. (Twice Amended) A method for assessing the presence of a target molecule in a cell or tissue sample comprising the steps of:

a. providing a microarray having a surface area comprising attached labeled probe molecules in quadrants, said labeled probe molecules including at least one nucleotide analog capable of fluorescence;

b. detecting fluorescence from said at least one nucleotide analog capable of fluorescence expressed within quadrants a first time;

c. applying a sample comprising unlabeled target sequences to the microarray;

d. providing a sufficient condition and time for target molecules to selectively pair with complementary labeled probe molecules;

e. detecting fluorescence from said at least one nucleotide analog capable of fluorescence expressed within quadrants a second time;

f. comparing the fluorescence expressed between the first time and the second time for each quadrant;

g. repeating steps c - f until levels of fluorescence decrease towards a level approaching [approach] zero and/or about background levels; and

h. the difference between fluorescence in that of step f and that of step c [identifying a] providing target/probe pair quantification.

17. (Twice Amended) A method for quantifying the amount of a target molecule in solution comprising the steps of:

a. providing a first substrate having a surface area comprising a known number of labeled probe molecules, said labeled probe molecules include at least one nucleotide analog capable of fluorescence;

b. detecting a first level of nucleotide analog fluorescence expressed by the labeled probe molecules on the first substrate;

c. contacting the first substrate with a volume of sample containing unlabeled target nucleotide sequences;

d. providing a sufficient condition and time for unlabeled target molecules to selectively pair with the labeled probe molecules;

e. removing the first substrate and detecting the level of nucleotide analog fluorescence expressed by said known number of labeled probe molecules after exposure to the sample containing unlabeled target molecules;

f. where the level of nucleotide analog fluorescence expression of the first substrate is substantially reduced to levels substantially similar to background levels, repeating steps a. through e. with subsequent substrates, having surface areas comprising known numbers of labeled probe molecules; and

g. calculating the amount of target molecule in the volume of sample by adding the known number of labeled probe molecules present on the first substrate and subsequent substrates contacted with the sample, wherein the levels of nucleotide analog fluorescence expression of the substrates are reduced to a level approaching zero relative to the levels prior to contacting the sample, whereby said amount of target molecule is quantified.

18. (AMENDED)The method of claim [10] 17, wherein the level of label expression is evaluated using a flow cytometer.

20. (Twice Amended) A method for monitoring the hybridization of target and probe by complementation, comprising :

a. incorporating fluorescent nucleotide analogs into probes;

b. detecting a first level of fluorescence emanating from probes of step a;

d. hybridizing a target with said probes thereby forming a probe-target complex;

e. detecting a second level of fluorescence emanating from said probe-target complex after hybridization of probe and target;

f. comparing the first and second levels of fluorescence between that of step b and that of step e, and wherein said difference between second and first levels is less than said first level of step b;

g. washing of unhybridized target; [and]

h. repeating steps d - g until the difference between the first and second levels of fluorescence approaches approximately zero and/or about background levels; and

i. quantifying the amount of target based upon said target's hybridization and subsequent quenching of said first level of fluorescence toward a level approaching zero.

22. (Thrice Amended) A method for monitoring the hybridization of a probe and a target comprising, providing a fluorescently labeled probe, said fluorescence being provided by a nucleotide analog capable of fluorescence and is incorporated, thereby providing a detectable first level of fluorescence and providing a detectable second level of fluorescence when the labeled probe is hybridized to a complementary unlabeled target, wherein the second level is

lower than the first level and approaches zero, said decrease in fluorescence quantifying the amount of complementary unlabeled target.

23. (Thrice Amended) A method for monitoring the hybridization of a probe and a target comprising supplying a fluorescently labeled probe, said fluorescently labeled probe being fluorescent due to the incorporation of at least one nucleotide analog thereby providing a detectable first level of fluorescence, and providing a detectable second level of fluorescence when the labeled probe is hybridized to a complementary unlabeled target, wherein the second level is significantly lower than the first level and said second levels of fluorescence approach zero and/or about background levels.

25. (Thrice Amended) A method for monitoring the hybridization of a probe and a target comprising supplying a fluorescently labeled probe, said fluorescently labeled probe being fluorescent due to the incorporation of at least one nucleotide analog capable of fluorescence, thereby providing a detectable first level of fluorescence, and a detectable second level of fluorescence when the labeled probe is hybridized to a complementary unlabeled target, wherein the second level is approximately zero and the first level is greater than zero, and utilizing said reduction of fluorescence to approximately zero for quantifying said complementary unlabeled target.

29. (Thrice Amended) A substrate having a known and quantified plurality of probes, wherein said probes are fluorescently labeled by incorporation of at least one nucleotide analog, the labeled probe providing a detectable first level of fluorescence, and when hybridized to a complementary target having no nucleotide analogs incorporated therein, providing a second level of fluorescence, wherein the second level approaches zero, and wherein said known and quantified plurality of probes provides for quantification of said complementary target.

31. (Twice Amended) A substrate having a surface area, the surface area comprising attached and quantified labeled probe molecules, said probe further comprising a fluorescent label, said fluorescent label including at least one nucleotide analog incorporated as part of a nucleotide sequence defining said labeled probe molecules.

34. (Amended) The method of claim [33] 31 whereby the labeled probe molecules are nucleotide analogs including 2-amino purine for adenosine or guanine; ribonucleoside or 2,6-diamino ribonucleoside, formycin A, formycin B, oxyformycin B, toyocamycin, sangivamycin, pseudoouridine, showdomycin, minimycin, pyrazomycin, 5-amino-formycin A, 5-amino-formycin B or 5-oxo-formycin A for adenosine; 4-amino-pyrazolo [3,4d] pyrimidine, 4,6-diamino-pyrazolo [3,4d] pyrimidine, 4-amino-6-oxo-pyrazolo [3,4d] pyrimidine, 4-oxo-pyrazolo [3,4d] pyrimidine, 4-oxo-6-amino-pyrazolo [3,4d] pyrimidine, 4,6-dioxo-pyrazolo [3,4d] pyrimidine, pyrazolo [3,4d] pyrimidine, 6-amino-pyrazolo [3,4d] pyrimidine or 6-oxo-pyrazolo [3, 4d] pyrimidine for cytosine or thymidine

35. (Amended) The substrate of claim [33] 31 whereby the incorporated nucleotide analog is 2-aminopurine replacing adenosine or guanine nucleotides.

39. (Amended) The [method] substrate of claim 1 whereby the incorporated nucleotide analog is 2-aminopurine replacing at least one endemic adenosine or guanine nucleotide.